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Commentary

Electronic cigarettes: The road ahead

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ABSTRACT

Electronic cigarettes (e-cig) are proliferating in the world's lucrative nicotine delivery market at an alarmingly fast pace. E-cig are aggressively marketed as an alternative to conventional tobacco cigarettes, although very little is known about the health consequences of e-cig use. Chemical analysis of e-cig vapor/liquid has shown that many toxicants and carcinogens present in cigarette smoke are also found, albeit generally in lower concentrations, in a wide range of e-cig products. Notwithstanding the presence of toxicants and carcinogens in e-cig products, the biological effects of exposure to these contaminants have not been determined in e-cig users. The ongoing research and future investigations on e-cig initiation, use, perceptions, dependence, and toxicity are expected to provide empirical evidence that can be used to inform the general public, scientific community, and regulatory authorities of the health risks/benefits associated with e-cig use. This information will help stimulate scientists in the field of tobacco research, as well as assist the regulatory agencies in making scientifically based decisions on the development and evaluation of regulations on tobacco products to protect the public's health. Finding the scientific underpinnings for the health risks/benefits of e-cig use can impact millions of people who are increasingly turning to e-cig as a replacement for or complement to conventional tobacco cigarettes.

The first modern electronic cigarettes (e-cig) were invented and patented by a Chinese pharmacist, Hon Lik, in 2003 (Pauly et al., 2007). The following year, this invention was introduced to the market as an alternative nicotine delivery device (Gardiner, 2013). E-cig consist of a mouthpiece comprised of a liquid-filled cartridge, which contains concentrated flavors, humectant (i.e., propylene glycol, vegetable glycerin, and/or polyethylene glycol 400), and optionally, variable concentrations of nicotine (Schaller et al., 2013). An atomizer equipped with a microchip-controller, sensor, and heater powered by a battery converts the liquid inside the cartridge into vapor that mimics cigarette smoke, with a red LED simulating a burning cigarette tip. In newer models of e-cig, the cartridge and atomizer are combined into a single unit, called a 'cartomizer'. Used e-cig cartridges or cartomizers can be replaced or refilled with 'e-juice' or 'e-fluid', which is readily available from the e-cig manufacturers or third party vendors (Gardiner, 2013). Due to lack of standardization in the manufacture and quality control of e-cig and refill products, there is, however, considerable variation in performance among different e-cig brands as well as within the same brand (Goniewicz et al., 2013, 2014a; Trtchounian et al., 2010).

Because e-cig employ heating to vaporize tobacco/nicotine products as opposed to burning to generate smoke, these products were launched as a less unhealthy alternative to regular tobacco cigarettes, although current advertising messages are more subtle and implicit (Cahn and Siegel, 2011; Palazzolo, 2013; Schaller et al., 2013; Westenberger, 2009). However, chemical analysis of e-cig vapor/liquid has shown that many toxicants and carcinogens present in cigarette smoke are also detectable, albeit generally at lower levels, in various e-cig products (Goniewicz et al., 2014b; Kim and Shin, 2013; McAuley et al., 2012; Schaller et al., 2013; Westenberger, 2009; Williams et al., 2013). For example, the Food and Drug Administration (FDA) testing of two brands of e-cig, including 18 cartridges of various flavors and nicotine content, showed mislabeling or inaccurate labeling of the nicotine quantity, and detectable levels of known carcinogens, such as tobacco-specific nitrosamines, and other contaminants suspected of being harmful to humans, e.g., anabasine, myosmine, β-nicotyrine, and diethylene glycol (Westenberger, 2009). Goniewicz et al. (2014b) confirmed the presence of tobacco-specific nitrosamines (N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)), carbonyl compounds (formaldehyde, acetaldehyde, acrolein, and o-methylbenzaldehyde), volatile organic compounds (toluene and p,m-xylene), and metals (cadmium, nickel, and lead) in e-cig aerosol generated from 12 different brands. The average ratios of the detected chemicals in e-cig aerosol to those in cigarette smoke were 1:380 for NNN, 1:40 for NNK, 1:9 for formaldehyde, 1:450 for acetaldehyde, 1:15 for acrolein, and 1:120 for toluene. Williams et al. (2013) quantified the level of 22 elements, including three elements

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(lead, nickel, and chromium) identified by the FDA as 'harmful or potentially harmful to humans' in e-cig aerosol prepared from a leading brand. Whereas the detected levels of lead and chromium were within the ranges known for conventional cigarette smoke, nickel concentrations were 2–100 times higher than those reported for Marlboro brand cigarette smoke. To put the chemistry of contaminants in e-cig aerosol/liquid into context, Burstyn (Burstyn, 2014) reviewed over 50 publications and concluded that there is no evidence that vaping causes inhalable exposure to contaminants at levels that would warrant health concerns by the standards used to ensure safety in workplaces. However, Burstyn acknowledged that e-cig aerosol as a whole (contaminants plus declared ingredients) creates personal exposure that would justify surveillance of health among e-cig users (Burstyn, 2014). Although the empirical evidence on the presence of contaminants in e-cig aerosol/liquid is being interpreted differently by the endorsers and opposers of these products, one may cautiously surmise on the grounds that there is no minimal threshold of toxicity for carcinogens (a generally accepted assumption).

As a new-generation nicotine delivery system, e-cig are rapidly gaining acceptance in the United States and many parts of the world (Abrams, 2014; Palazzolo, 2013; Yamin et al., 2010). Currently, the global e-cig market is worth $6B (billion). In the United States, the estimated e-cig retail sales approached $2B at the end of 2013, and will rise to $10B by 2017. It is anticipated that e-cig sales will surpass that of conventional tobacco cigarettes by 2023 (Herzog, 2013). According to a study by the Centers for Disease Control and Prevention (CDC), nearly 6% of all U.S. adults have used e-cig, and approximately 21% of American adult smokers (i.e., an estimated population of 45 millions) have tried e-cig in the past ((CDC), 2013). The Tobacco Vapor Electronic Cigarette Association claims that around 4 million Americans are e-cig users (TVECA Association). The alarming trend for e-cig use also extends to minors as the number of U.S. middle and high school students who tried e-cig more than doubled between 2011 and 2012, rising from 4.7% to 10%. In 2012, over 1.78 million middle and high school students nationwide have admitted to using e-cig. Most worryingly, 76.3% of youth who used e-cig within the past 30 days also smoked regular tobacco cigarettes in the same period (i.e., dual use) ((CDC), 2013). Opponents of the e-cig use argue that the rising popularity of e-cig among minors is particularly concerning because these products may serve as a 'gateway' to using conventional tobacco products. Because the vast majority of smokers pick up the habit as teenagers (Nelson, 2014), the availability of e-cig to impressionable teens is worrisome because it may ultimately lead to smoking and/or using other tobacco products. The proponents, however, contend that (young) smokers are more likely to experiment with e-cig than nonsmokers, as shown in recent survey-based studies (Goniewicz and Zielinska-Danch, 2012; Pepper et al., 2013; Sutfin et al., 2013). Opposers of e-cig use also draw attention to the increasing trend of dual use claiming that smokers may use e-cig to temporarily alleviate their craving for tobacco cigarettes, especially in settings where smoking is prohibited. Under such assumption, dual users may take advantage of e-cig as a 'quick fix', and maintain their smoking status without feeling the need to quit smoking. However, e-cig advocates argue that dual users are likely to gain health benefits from smoking fewer tobacco cigarettes. Notwithstanding, the risks for smoking-associated cardiovascular diseases and cancer are more dependent on smoking duration than smoking intensity; in other words, how long one smokes is a better predictor of risk than how many cigarettes she/he smokes (Bjartveit and Tverdal, 2005). Thus, the net benefits of smoking fewer conventional cigarettes by some dual users is likely to be outweighed by the greater harm caused by smoking of the overall population (Hampton, 2014). A recent clinical trial in New Zealand showed that quit rates among smokers who used e-cig were not statistically significantly different from those who used nicotine patches (Bullen et al., 2013). An Italian study, however, reported that the use of e-cig substantially reduced cigarette consumption among smokers who did not intend to quit (Polosa et al., 2011). Conversely, another Italian trial showed no consistent differences in cigarette consumption or quit rates among smokers who used e-cig with or without nicotine (Caponnetto et al., 2013). The World Health Organization (WHO) stated that as of July 2013, the efficacy of e-cig in aiding smoking cessation had not been demonstrated scientifically, and recommended that "*consumers should be strongly advised not to use e-cig until a reputable national regulatory body has found them safe and effective*" ((WHO), 2013).

With the enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) (Public Law 111–31) in 2009, the FDA was granted authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors (http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM237080.pdf). Within the framework of the FSPTCA, the FDA and the National Institutes of Health (NIH) have formed an interagency partnership to foster research relevant to tobacco regulatory science, and identified multiple research priorities, including e-cig initiation, use (including transition to other tobacco products and multiple use), perceptions, dependence, and toxicity (https://prevention.nih.gov/tobacco-regulatory-science-program/research-priorities). The ongoing research and future investigations on these topics are expected to provide empirical evidence that can be used to inform the general public, scientific community, and regulatory authorities of the health risks/benefits associated with e-cig use. Not only will this information help generate further interests for scientists in the field of tobacco research, but it will also assist the regulatory agencies in making scientifically based decisions on the development and evaluation of regulations on tobacco products to protect the public's health. Finding the scientific underpinnings for the health risks/benefits of e-cig use can impact millions of people who are increasingly turning to e-cig as a replacement for or complement to conventional tobacco cigarettes.

As the new generation of 'vapers' joins the conventional 'smokers', the scientific community is tasked with demystifying whether e-cig is a viable means to smoking cessation and/or harm reduction. It will be fitting to see the new generation of scientists undertake this challenging task, and help inform 'vapers' of the health risks/benefits associated with e-cig use. After all, the explosion in popularity of e-cig and the emergence of a fiercely passionate subculture, whose members are mostly young and youthful 'vapers', are best met by aspiring new scientists who can build upon their predecessors' work in the field of tobacco research. The time has arrived now; no matter how daring this venture may look, we should embark upon it. Let's start uncovering the mysteries of e-cig.

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Conflict of interest statement

All the authors declare no conflict of interest.

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